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Interaction Between Sodium Intake, Angiotensin II, and Blood Pressure as a Cause of Cardiac Hypertrophy

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Cardiac hypertrophy is common in hypertension but its development is influenced by angiotensin II, sodium intake aldosterone, and the time of day blood pressure (BP) is elevated. This study examined and compared cardiac hypertrophy in the 2 kidney-1 clip (2K-1C) and 1 kidney-1 clip (1K-1C) Goldblatt models of hypertension. Blood pressure was measured by telemetry in a selected group of rats. Rats were placed on a high (4%) or reduced (0.2%) salt intake and were given captopril (75 mg/kg per day) or losartan (10 mg/kg per day). Appropriate sham-operated and untreated controls were used.

Cardiac hypertrophy was greater in the 1K-1C than in the 2K-1C model. Day and sleep BP were also higher. In the 2K-1C model BP was lower on the reduced salt intake and BP decreased with captopril in both reduced and high salt groups. Cardiac weight and index decreased significantly only in the reduced salt and captopril group and was less than the size before treatment. In the 1K-1C model captopril caused all BP measures to decrease in the reduced salt group but had no significant effect in the high salt group. Cardiac weight and index were reduced only in the reduced salt + captopril group and cardiac weight was less than the pretreatment control. Losartan had a similar effect in the 1K-1C model to that achieved with captopril. The responses achieved correlated in part with renin status and dependency level.

There is no prime determinant of cardiac hypertrophy. Blood pressure, sodium intake, and hormonal status are all important. It is postulated that the common pathway may be alterations in cell composition that signal the nucleus to increase cell growth. Am J Hypertens 2001; 14:914–920 © 2001 American Journal of Hypertension, Ltd.

Key Words: Angiotensin II, cardiac hypertrophy, hypertension, Goldblatt hypertension, angiotensin converting enzyme inhibitors, AT_1 receptor blockers.

Cardiac hypertrophy is an independent predictor of cardiac morbidity and mortality and is commonly present in people and animals with high blood pressure.[1,2] However, it is unclear what factors are the major contributors to this cardiac enlargement. High blood pressure (BP) by increasing cardiac wall stress or by increased cardiac work undoubtedly contributes to its development.[3–5] However, other factors are clearly of importance.[6] Angiotensin II elevates BP but also has direct effects on cardiocytes in vivo and in culture, increasing the production of various mRNAs, which could be the cause of cardiac enlargement. But if BP elevation was prevented in rats, cardiac hypertrophy did not result.[7] These results were not reproduced by other investigators[8] who claim that angiotensin II can cause left ventricular hypertrophy (LVH) independent of BP elevation. In volume load hypertrophy, which causes both right and left ventricular enlargement, blockade of the renin system either by angiotensin converting enzyme (ACE) inhibitors or by AT_1 receptor blocking drugs causes resolution of the enlargement of both ventricles.[9,10] Another factor causing LVH is increased sodium chloride intake.[11] Rats given extra NaCl develop cardiac hypertrophy with no obvious increase in BP. However, it is possible that BP may have been elevated at night because it was not assessed by telemetry. In these salt-loaded models renin and angiotensin II levels would be low, suggesting that there may be an interaction between NaCl intake and angiotensin II at the cellular level. A low NaCl intake reduces the hypertrophy caused by angiotensin II, whereas a high NaCl intake appears to augment the hypertrophy response with little effect on BP.[12,13] Aldosterone has also been reported to cause LVH, but its interaction with sodium intake and angiotensin II levels has not been fully studied.[14]

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A number of factors may cause resolution of LVH. Thus, it has been reported that bradykinin accumulation in the heart caused by low-dose ACE inhibitors may allow resolution of LVH without an effect on BP.[15] It has also been suggested that angiotensin II acting through the angiotensin type II receptor may prevent the usual pressor and chronotrophic effects of angiotensin II.[16]

This study was set up to observe the interactions between BP (assessed by telemetry), sodium intake, and inhibition of converting enzyme or blockade of the AT_1 receptor in two rat models of Goldblatt hypertension. Blood pressure in the 2 kidney-1 clip (2K-1C) model is initially a renin-dependent model and it has been stated that the renin dependency diminishes with time. The 1 kidney-1 clip (1K-1C) model of hypertension can be either renin dependent or renin independent according to the sodium intake.

Methods

The experiments were performed on Wistar rats obtained from IFFA-Credo, Domaine des Oncins, 69210 L'Arbresle, France.

Blood Pressure Assessment

Blood pressure was measured continuously by telemetry in a number of rats (Griffiths C, Morgan TO, Delbridge LMD, unpublished data).[17] In general, one telemetry rat was used as a surrogate for four experimental rats and the animals were treated in an identical fashion except that a telemeter was inserted into the abdominal aorta 2 weeks before hypertension was created (concurrent study). To obtain confirmatory data related to the effect of diet and drugs on BP, a supplementary procedure was undertaken at the end of the study. The groups of rats with telemeters in place were randomly assigned to receive each of the therapeutic procedures for a 1-week period. The data from day 4 to day 7 of each intervention was used to assess the response to that therapy (crossover study). While the telemeters were in place, BP was sampled over a 10-sec interval every 10 min and the BP was accumulated and assessed using the Dataquest system (Data Science International, St Paul, MN).

Cardiac Hypertrophy and BP in the Experimental Rat Group

Twenty-four hours before the end of the study rats were anesthetized with fluothane and a cannula was inserted into the femoral artery and exteriorized at the back of the head. The rats were allowed to recover and the next day BP was recorded in a conscious rat during a 1-h interval. Rats in the experimental group that had a mean arterial pressure <130 mm Hg were excluded from the study. Captopril was not administered after the cannula was inserted and thus the BP recording was made approximately 36 to 40 h after the last dose of captopril. Observations in rats with telemeters indicated that BP had returned to untreated levels by this time. After BP was measured rats were killed and the heart removed. The great vessels and the atria were removed and the heart was blotted dry and weighed. The weight was recorded in milligrams but was also factored by the body weight of the rat to give a cardiac index.

Renin Status and Angiotensin Dependency

Plasma renin concentration was measured on a sample of blood collected by orbital puncture under light ether anesthetic 2, 4, and 8 weeks after a clip was placed on the renal artery. The renin concentration was determined by adding 24-h nephrectomized rat plasma and the angiotensin I generated was measured by radioimmunoassay. The responsiveness of the BP was determined by giving an intraperitoneal injection of captopril (10 mg/kg) to the rats with telemeters inserted. The BP was sampled during a 10-sec interval every 5 min for the next 2 h and the peak decrease in BP determined. This procedure was done in rats 2, 4, and 8 weeks after the Goldblatt hypertension was created.

Model 1: 2K-1C Goldblatt Hypertension

Wistar rats weighing approximately 300 g were anesthetized and a 0.20-mm silver clip was placed around the left renal artery. The rats were allowed to recover and were placed on their normal diet for 3 weeks. A group of rats had a sham operation performed. At 3 weeks a group of the sham-operated and 2K-1C rats were killed and cardiac size assessed as stated above. Sham-operated rats were divided into two groups and placed on a reduced (0.2%) or high (4%) NaCl diet. The 2K-1C rats were divided into two groups and placed on the high or reduced salt intake. The 2K-1C rats were further divided into two groups and one group on the high or reduced salt intake was given captopril in the drinking water with the concentration adjusted to give an intake of 75 mg/kg per day. When rats were allocated to groups this was done in a stratified manner to provide groups of approximate equal weights. Rats were treated for 4 weeks and at the end of that time were killed and cardiac size measured.

Model 2a: 1K-1C Goldblatt Hypertension

Wistar rats of approximately 275 g had their right kidney removed and a 0.20-mm silver clip placed around their left renal artery. They were allowed to recover. Groups of rats were treated in a similar manner to the 2K-1C model. At the end of the study the rats were treated as stated above.

Model 2b: 1K-1C

This group was similar to model 2a with the following difference. In this model there were no sham-operated or untreated controls. Three weeks after hypertension was created rats were placed on a high or reduced NaCl intake

Table 1. Chronic response of systolic blood pressure (mm Hg) to captopril (75 mg/kg/day) in rats on a high (4%) and reduced (0.2%) sodium chloride intake

	Untreated (Week 3)	High Salt 4%		Reduced Salt 0.2%	
		Control	Captopril	Control	Captopril
2K-1C					
n	8	7	7	7	6
24 h	176	188	166	162	132*
Awake 20:00–24:00	188	196	175	175	146*
Sleep 08:00–12:00	152	172	151	143	110*
1K-1C					
n	8	6	6	6	6
24 h	202	203	190	186	136*
Awake 20:00–24:00	214	212	200	204	144*
Sleep 08:00–12:00	195	192	179	158*	113*

SEM were between 4 and 8 for all measurements.

For all blood pressure measurements in the 2K-1C model; high salt > high salt + Capt = reduced salt > reduced salt + Capt, $P < .09$ by ANOVA and paired *t* test with Bonferroni correction.

* $P < .001$ compared with all values to the left by ANOVA and paired *t* test with Bonferroni correction.

and given losartan (10 mg/kg per day) intraperitoneally at 08:00 daily for 4 weeks. The two groups were then studied as stated above.

Statistical Analysis

The results are presented with the mean and SEM. The comparison in the crossover study of the response in BP was made by ANOVA and by paired *t* tests with Bonferroni correction. The other data was analyzed by one- or two-way ANOVA as appropriate. For each ANOVA a post hoc analysis was performed using the Student-Newman-Keuels method.

Results

2K-1C Goldblatt Hypertension

Telemetry BP Telemetry was not performed on the sham-operated rats in this study and values for sham-operated rats on a normal diet are from a previous study in rats of the same strain and size[17] (24 h, 115 ± 3 mm Hg; awake, 131 ± 5 mm Hg; sleep, 108 ± 3 mm Hg). At the end of the 3-week period BP was elevated in all eight rats in which a clip had been placed around the left renal artery (Table 1). The results in the concordant study and the crossover study were similar. Only results from the crossover study are shown (Table 1). Systolic BP was highest in the 2K-1C Goldblatt rats on a high salt (4%) intake. This was the situation for 24 h, awake, and sleep BP. In rats on a high and reduced salt intake captopril (75 mg/day) caused a significant decrease in all pressures measured. The lowest BP was achieved with reduced salt and captopril (Table 1). The decrease in 24-h BP when captopril was given to rats on a reduced salt diet was greater than when captopril was given to rats on a high salt intake (30 ± 4 mm Hg *v* 22 ± 3 mm Hg, $P = .01$).

Plasma Renin and Angiotensin Dependency of BP A group of untreated 2K-1C Goldblatt rats with BP telemeters inserted were followed for 8 weeks on a 0.2% and 4% NaCl intake. The acute response to an intraperitoneal injection of captopril (10 mg/kg) was measured. Rats on 0.2% NaCl intake had a lower systolic BP than rats on 4% NaCl intake (Table 2). The decrease in BP on the two diets did not differ but the systolic BP at time of peak response to captopril was lower in the rats on 0.2% NaCl (147 ± 3 mm Hg *v* 173 ± 5 mm Hg, $P < .001$). There was no difference in response with time. Plasma renin concentration was higher on the 0.2% NaCl intake and on both 0.2% and 4% NaCl dietary intakes it tended to decline with time (Table 2).

Cardiac Size At week 3 sham-operated rats were divided into three groups. One group was killed and the other two placed on a high or reduced salt intake, respectively, for 4 weeks. The rats grew to a similar extent (Table 3). Cardiac weight and cardiac index tended to be greater in the rats on a high salt intake but changes were of marginal significance. At week 3, 40 2K-1C Goldblatt rats were divided into five groups. One group was killed and the other four groups treated as indicated (Table 3). The reduced salt + captopril group did not grow as well as the other groups ($P < .05$). When BP was measured in the experimental rats by an intra-arterial cannula at the end of the experiment five rats did not meet our criteria for hypertension and were excluded from analysis (Table 3). In rats on a reduced salt diet + captopril, cardiac size and index were lower than in all other treatment groups and were less than in the untreated group at week 3 indicating cardiac involution (Table 3). The values were not different from sham-operated controls. In rats on a high salt intake and captopril there was a small reduction in heart weight and cardiac index compared to the untreated 2K-1C rats on a high salt intake ($P < .05$). In rats with 2K-1C Goldblatt

Table 2. Renin status of the different groups and dependency of blood pressure on angiotensin II

	Plasma Renin Concentration (pmol A_1/mL/h)	Systolic Blood Pressure (mm Hg)		
		Initial	Fall	Lowest BP
2K-1C 0.2% NaCl				
2 weeks	6.4 ± 1.2	172 ± 6	32 ± 4	140 ± 5
4 weeks	6.8 ± 1.1	178 ± 5	31 ± 5	147 ± 5
8 weeks	3.9 ± 1.1	187 ± 7	34 ± 3	153 ± 4
2K-1C 4% NaCl				
2 weeks	1.4 ± 0.8	193 ± 7	23 ± 4	170 ± 6
4 weeks	1.2 ± 0.6	198 ± 6	25 ± 4	173 ± 4
8 weeks	1.0 ± 0.3	202 ± 9	28 ± 3	174 ± 7
1K-1C 0.2% NaCl				
2 weeks	4.4 ± 0.5	189 ± 7	56 ± 5	133 ± 5
4 weeks	4.1 ± 0.5	196 ± 8	52 ± 4	144 ± 6
8 weeks	4.9 ± 0.4	207 ± 6	61 ± 6	146 ± 4
1K-1C 4% NaCl				
2 weeks	0.4 ± 0.2	195 ± 6	12 ± 3	183 ± 5
4 weeks	0.5 ± 0.2	203 ± 4	8 ± 2	195 ± 5
8 weeks	0.4 ± 0.2	216 ± 6	11 ± 3	205 ± 6

BP = blood pressure.
Mean; SEM; $n = 4$.

hypertension on a high salt intake cardiac index and cardiac weight were higher than in the sham-operated or reduced salt–captopril-treated 2K-1C group. There was a trend for cardiac weight to be higher in this high salt group compared to rats on a high salt diet + captopril ($P < .05$) and those on a reduced salt diet ($P = .08$) (Table 3).

1K-1C Goldblatt Model

Telemetry BP Blood pressure was elevated in all rats at week 3. Two of the telemetry rats died during the study. Both were on a high salt intake, one on captopril and one on no drugs. The only group that had a large decrease in BP were the rats on a reduced salt intake that received captopril and the BP in these rats decreased toward the normal level. In the crossover study performed in the six remaining rats similar results were observed with the BP having the following order (lowest first), reduced salt + captopril, reduced salt, high salt + captopril, high salt. Captopril had only a minor effect on BP in the rats on a high salt intake (12 ± 4 mm Hg), but had an extremely

Table 3. Body weight, cardiac weight, and cardiac index in the various groups

		n	Body Weight (g)	Heart Weight (mg)	Cardiac Index (mg/g)
2K-1C					
Sham operated	(wk 3)	8	357 ± 6	771 ± 15	2.16 ± 0.05
High salt	(wk 7)	8	401 ± 6	890 ± 22	2.22 ± 0.06
Reduced salt	(wk 7)	8	399 ± 7	806 ± 18	2.02 ± 0.06
Experimental	(wk 3)	8	354 ± 5	948 ± 24	2.78 ± 0.05
High salt	(wk 7)	7*	381 ± 7	1120 ± 25	2.94 ± 0.06
High salt + Capt	(wk 7)	7*	392 ± 6	1027 ± 24	2.62 ± 0.06
Reduced salt	(wk 7)	6*	396 ± 7	1077 ± 21	2.72 ± 0.06
Reduced salt + Capt	(wk 7)	7*	365 ± 5	781 ± 23‡	2.14 ± 0.06‡
1K-1C					
Sham operated	(wk 3)	8	334 ± 6	731 ± 21	2.19 ± 0.05
	(wk 7)	8	373 ± 6	788 ± 23	2.14 ± 0.06
Experimental	(wk 3)	8	287 ± 6	1028 ± 28	3.58 ± 0.08
High salt	(wk 7)	4†	325 ± 12	1311 ± 24	4.03 ± 0.09
High salt + Capt	(wk 7)	7†	335 ± 9	1237 ± 35	3.69 ± 0.13
Reduced salt	(wk 7)	9	305 ± 9	1244 ± 17	4.08 ± 0.06
Reduced salt + Capt	(wk 7)	9	289 ± 5	826 ± 15§	2.86 ± 0.05§

Capt = captopril.
* These groups were 8 rats at allocation but 5 rats were excluded because they did not meet the hypertension criteria.
† 5 and 2 rats died in each of these groups and were smaller than those that survived.
‡ $P < .01$ compared to all other values in 2K-1C model and not different from sham-operated controls.
§ $P < .05$ compared to all other values in 1K-1C model but significantly higher than controls.
Statistical comparison with two-way analysis of variance with post hoc SNK correction.

Table 4. Effect of losartan on blood pressure and cardiac size in rats on a high and reduced salt diet with 1K-1C hypertension

	Losartan (10 mg/kg/day)		
	High Salt Intake	**Reduced Salt Intake**	***P***
n	4	4	
24-h BP*	198 ± 10	152 ± 7	<.001
Awake BP (20:00–24:00)	190 ± 12	121 ± 12	<.001
Sleep BP (08:00–12:00)	208 ± 15	168 ± 12	<.001
n	8	8	
Died	1	0	
Body weight (g)	345 ± 8	325 ± 6	
Heart weight (mg)	1415 ± 49	884 ± 36	<.01
Cardiac index (mg/g)	4.10 ± 0.13	2.72 ± 0.08	<.01

Abbreviation as in Table 2.
* BP levels are those during the crossover study.
P values with Bonferroni correction.

large effect on BP in rats on the reduced salt intake (50 ± 6 mm Hg).

Plasma Renin and Angiotensin Dependency of BP A group of untreated 1K-1C Goldblatt rats with telemeters inserted were followed for 8 weeks on a 0.2% and 4% NaCl intake. One rat on the high salt intake died at week 5. The acute response to an intraperitoneal injection of captopril (10 mg/kg) was measured (Table 2). There was no significant difference in BP on the 0.2% and 4% NaCl intake, but the decrease in BP with captopril was significantly greater ($P < .001$) in rats on 0.2% NaCl. The systolic BP at time of peak response in the rats on 0.2% NaCl (142 ± 4 mm Hg) was significantly lower ($P < .001$) than the BP in rats on 4% NaCl (204 ± 11 mm Hg). Plasma renin concentration in rats on 4% NaCl was very low and increased significantly on 0.2% NaCl (Table 2).

Cardiac Size By week 3, five rats that had a 1K-1C procedure had died and the remaining 44 rats were randomized to five groups matched for body weight. One group of eight rats were killed and the other four groups of nine animals were placed on their appropriate treatments (Table 3). During the 4 weeks of treatment seven rats died. Five were in the high salt group and two in the high salt + captopril group. All surviving rats met the criteria for hypertension assessed by intraarterial cannulation and were included in the analysis (Table 3). The rats with 1K-1C hypertension did not grow as rapidly as the sham-operated controls. The rats on the reduced salt intake did not grow as well as those on the high salt intake, but it is difficult to be certain of the importance of this difference as the rats that died in the high salt group were smaller than the others.

Cardiac weight and cardiac index were greater at week 7 compared to the value at week 3 in the reduced salt, high salt, and high salt + captopril group ($P < .01$). In the rats on a high salt intake given captopril there was a possible decrease in cardiac index and cardiac weight compared to the rats on a high salt intake. However, the high mortality in these groups makes comparison hazardous. In the group on a reduced salt intake + captopril the cardiac weight and cardiac index were lower than in the other three groups and were less than the values in the untreated group at week 3. However, the cardiac index was greater than in sham-operated controls.

1K-1C Goldblatt Hypertension Given Losartan

Four rats had telemeters inserted. The BP during the concordant study and in the crossover study at the end of the experimental study was lower in the reduced salt rats given losartan (Table 4). In the rats on a high salt intake + losartan the BP did not differ from the BP on a high salt intake in the previous study. Cardiac weight and cardiac index were lower in the rats on a reduced salt intake and losartan (Table 4). In rats on a high salt intake and losartan, cardiac weight and index was not different from untreated rats of the same age in the previous study.

Comparison Between the Two Models

In the untreated rats, 3 weeks after the surgical model was created, heart weight and heart index were greater in the 1K-1C model than in the 2K-1C model ($P < .01$). In the 1K-1C model there appeared to be a continuation of the increase in cardiac size as heart weight and cardiac index both increased. In the 2K-1C model it appeared that the hypertrophy was fully expressed by week 3 as there was no further increase in cardiac size.

Discussion

The BP levels in the two Goldblatt models were similar but cardiac hypertrophy in the 1K-1C model was greater than in the 2K-1C model. The second model is stated to be the angiotensin-dependent model and therefore, this dif-

ference is surprising and suggests that a factor present in the 1K-1C model is more important than angiotensin II. The 24-h mean BP, and in particular sleep BP, was higher in the 1K-1C model and this might contribute to the different degree of hypertrophy. Both models show circadian variation in BP and the difference between sleep and awake BP was greater in the 2K-1C model (36 mm Hg) than in the 1K-1C model (19 mm Hg), leading to a higher sleep BP in this later model. From previous studies,[17,18] it has been inferred that sleep BP is a more important determinant of LVH than other BP indices. Although there were differences in sleep BP, other explanations are possible.

In the 2K-1C model, blockade of the angiotensin system with ACE inhibitors caused a decrease in BP independent of the NaCl intake, although the final pressure achieved was lower in the rats on the reduced salt intake as well as captopril. The effect of reduced salt diet and ACE inhibition was at least additive. Cardiac size in the reduced salt + captopril group returned to a similar value as in sham-operated rats. In rats on a high salt intake + captopril there was a small decrease in cardiac weight but the cardiac weight and cardiac index were greater than in sham-operated controls and in the reduced salt and captopril group.

The 1K-1C model is often stated to be a volume-dependent model, or more correctly a sodium-retaining model, which leads to development of hypertension. However, there are clearly interactions between sodium retention and angiotensin II in the development and perpetuation of hypertension. In the 1K-1C model a significant reduction in BP toward the normal level was only obtained in rats on a reduced salt diet in which the action of angiotensin II was prevented. This reduction in BP occurred whether the system was blocked by ACE inhibitors or by an AT_1 receptor-blocking drug. Associated with the decrease in BP there was resolution of cardiac hypertrophy. Blood pressure and LVH were reduced in parallel, suggesting that the BP signal was of major importance (Fig. 1).

The dose of captopril or losartan used would be expected to prevent the effect of angiotensin II throughout the 24-h period. Despite this blockade cardiac hypertrophy persisted and therefore, it would appear that angiotensin II is not essential to allow persistence of cardiac hypertrophy. It is possible that AT_1 receptors are upregulated on a high salt intake or alternatively that despite blockade of plasma ACE there is still tissue conversion immediately adjacent to the AT_1 receptor and thus, blockade is not complete. However, in normotensive rats (Griffiths C, Morgan TO, Delbridge LMD, unpublished data), combined ACE inhibition and AT_1 blockade causes regression of cardiac size. This regression is prevented by a high salt intake, although BP still decreases, but not to the same extent. This suggests that angiotensin II may be important to maintain normal cardiac size and cause cardiocyte growth, but the effect of absence of angiotensin II can be prevented by a high salt intake.

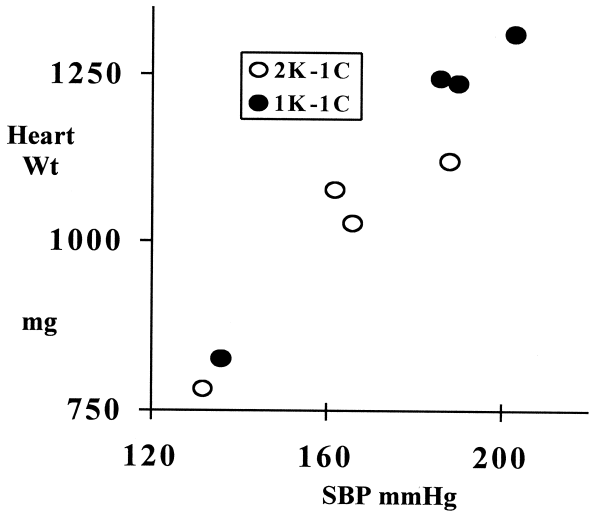

FIG. 1. Correlation between the mean 24-h blood pressure assessed by telemetry and the weight of the heart in the 2K-1C and the 1K-1C model in different diet and therapeutic regimes. Despite markedly different hormonal environments (eg, high bradykinin, low plasma angiotensin II, unopposed AT_2 action) there was a strong correlation between 24-h blood pressure and cardiac weight.

Bradykinin has been implicated as an important factor that can cause resolution of cardiac hypertrophy.[15] The present data are contradictory to the hypothesis that bradykinin is of critical importance because with high dose captopril on a high salt intake there was no resolution of LVH and bradykinin levels would have been expected to be elevated. It must be emphasized that these results do not mean that bradykinin may not contribute in certain circumstances to resolution or prevention of LVH, but it is not of critical importance.

From this and our previous studies (Griffiths C, Morgan TO, Delbridge LMD, unpublished data),[12,13,17] the following conclusions can be drawn. Elevated BP probably working by way of wall stress or by an acute increase in cardiac work is important to initiate the signal that leads to LVH. However, similar levels of BP may have different results dependent on the time of day. An elevated BP during the sleep (and possibly the awakening) period appears to more clearly cause LVH. If BP is normalized for 24 h or even during the sleep period, cardiac hypertrophy resolves. In no situation did we obtain significant reduction in cardiac hypertrophy unless BP was normalized either completely or during the sleep period. The role of angiotensin II is complex. In rats on a reduced salt intake it appears to be essential to maintain normal cardiocyte and possibly somatic growth. However, this requirement is overcome if rats are on a high salt intake. When on a high salt intake the prevention of angiotensin II effect by ACE inhibition or by AT_1 receptor blockade or by their combination (Griffiths C, Morgan TO, Delbridge LMD, unpublished data) has little or no effect on cardiac size.

There has been a recent tendency to regard angiotensin II as being all important related to BP and its inherent complications, but the initial work relating morbidity to renin levels clearly emphasized the importance of sodium in this relationship.[19] The exact mechanism that controls these changes is not clearly determined but may relate to effects that angiotensin II and sodium balance have on the ionic composition of different cells.[20–22] Thus, angiotensin II and high sodium intake may both alter cellular electrolyte composition in a similar way but by different mechanisms and thus additive adverse consequences may result. Likewise, prevention of the adverse effects of angiotensin II may not result from its blockade if a person or animal is on a high salt intake. Similarly, adverse effects of angiotensin II may not occur on a reduced salt intake because the critical changes in cellular electrolyte concentration may not result. The exact electrolyte changes of importance are not clear and are probably multifactorial.[21,22] However, this study reinforces the importance of the interaction of BP, sodium, and angiotensin II in determining the final response.

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References

1. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP: Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. N Engl J Med 1990;322:1561–1566.
2. Cooper RS, Simmons BE, Castaner A, Santhanam V, Ghali J, Mar M: Left ventricular hypertrophy is associated with increased mortality independent of ventricular function and number of coronary arteries severely narrowed. Am J Cardiol 1990;65:441–445.
3. Yamazaki T, Komuro I, Kudoh S: Angiotensin II partly mediates mechanical stress induced cardiac hypertrophy. Circ Res 1995;77: 258–265.
4. Sadoshima J, Xu Y, Slayter HS, Izumo S: Autocrine release of angiotensin II mediates stretch induced hypertrophy of cardiac myocytes. Cell 1993;75:977–984.
5. Drayer J, Weber MA, De Young DL: Blood pressure as a determinant of cardiac left ventricular muscle mass. Arch Int Med 1983; 142:90–92.
6. Morgan HE, Baker KM: Cardiac hypertrophy. Mechanical, neural and endocrine dependence. Circulation 1991;83:13–25.
7. Griffin SA, Brown WC, MacPherson F, McGrath JC, Wilson VG, Korsgaard N, Mulvany MJ, Lever AF: Angiotensin II causes vascular hypertrophy in part by a non-pressor mechanism. Hypertension 1991;17:626–635.
8. Kim S, Ohta K, Hamaguchi A, Yukimura T, Miura K, Iwao H: Angiotensin II induces cardiac phenotypic modulation and remodeling in vivo in rats. Hypertension 1995;25:1252–1259.
9. Ruzicka M, Yuan B, Harmsen E, Leenen FH: The renin-angiotensin system and volume overload-induced cardiac hypertrophy in rats: effects of angiotensin converting enzyme inhibitors versus angiotensin II receptor blocker. Circulation 1993;87:921–930.
10. Iwai N, Shimoike H, Kinoshita M: Cardiac renin-angiotensin system in the hypertrophied heart. Circulation 1996;92:2690–2696.
11. Yuan BX, Leenen FH: Dietary sodium intake and left ventricular hypertrophy in normotensive rats. Am J Physiol 1991;261:H1397–H1401.
12. Morgan T, Brunner H, Aubert J-F, Connell P: The relationship of blood pressure to cardiac hypertrophy: experimental studies in rats. Clin Exp Hypertens 1997;19:827–841.
13. Morgan TO, Aubert J-F, Wang Q: Sodium, angiotensin II, blood pressure and cardiac hypertrophy. Kidney Int 1998; 54(suppl 67): S213–S215.
14. Young M, Head G, Funder JW: Determinants of cardiac fibrosis in experimental hypermineralocorticoid states. Am J Physiol 1995; 269:E657–E662.
15. Linz W, Schφlkens BA: A specific B2-bradykinin receptor antagonist HOE 140 abolishes the antihypertrophic effect of ramipril. Br J Pharmacol 1992;105:771–772.
16. Masaki H, Kurihara T, Yamaki A, Inomata N, Nozawa Y, Mori Y, Murasawa S, Kizima K, Maruyama K, Horiuchi M, Dzau VJ, Takahashi H, Iwasaka T, Inada M, Matsubara H: Cardiac-specific overexpression of angiotensin II AT2 receptor causes attenuated response to AT1 receptor-mediated pressor and chronotropic effects. J Clin Invest 1998;101:527–535.
17. Morgan TO, Brunner HR, Aubert J-F, Wang Q, Griffiths C, Delbridge L: Cardiac hypertrophy depends upon sleep blood pressure: a study in rats. J Hypertens 2000;18:445–451.
18. Morgan T, Griffiths C, Delbridge L. Wall stress, angiotensin II and left ventricular hypertrophy, *in* Epstein M, Brunner H (eds): Angiotensin II Receptor Antagonists. Philadelphia, Hanley & Belfus, 2000, pp 223–234.
19. Brunner HR, Laragh JH, Baer L, Newton MA, Goodwin FT, Krakoff LR, Bard RH, Bühler FR: Essential hypertension: renin and aldosterone, heart attack and stroke. N Engl J Med 1972;286:441–449.
20. Resnick L: The cellular ionic basis of hypertension and allied clinical conditions. Prog Cardiovas Dis 1999;42:1–22.
21. Resnick LM, Gupta RK, DiFabio B, Barbagallo M, Mann S, Marion R, Laragh JH: Intracellular ionic consequences of dietary salt loading in essential hypertension: relation to blood pressure and effects of calcium channel blockade. J Clin Invest 1994;94:1269–1276.
22. Resnick LM, Gupta RK, Sosa RE, Corbett ML, Laragh JH: Intracellular pH in human and experimental hypertension. Proc Natl Acad Sci USA 1987;84:7663–7667.